CHAPTER 3

Cardiovascular Disease and the U.S. Army's Role in Combating It

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INTRODUCTION

The 20th century was an era of great technological advancement along with enormous improvement in the quality of life. But there has been a downside. Extensive epidemiological evidence demonstrates that cardiovascular disease (CAD) is increasing in industrialized societies and that its prevalence rose throughout most of the century. Cardiovascular disease remains the leading cause of death in the United States. In 1997 over 450,000 males and 505,000 females died as a result of cardiovascular disease (Tables 1&2).

Table 1. Causes of Male Deaths in the U.S. (1997)

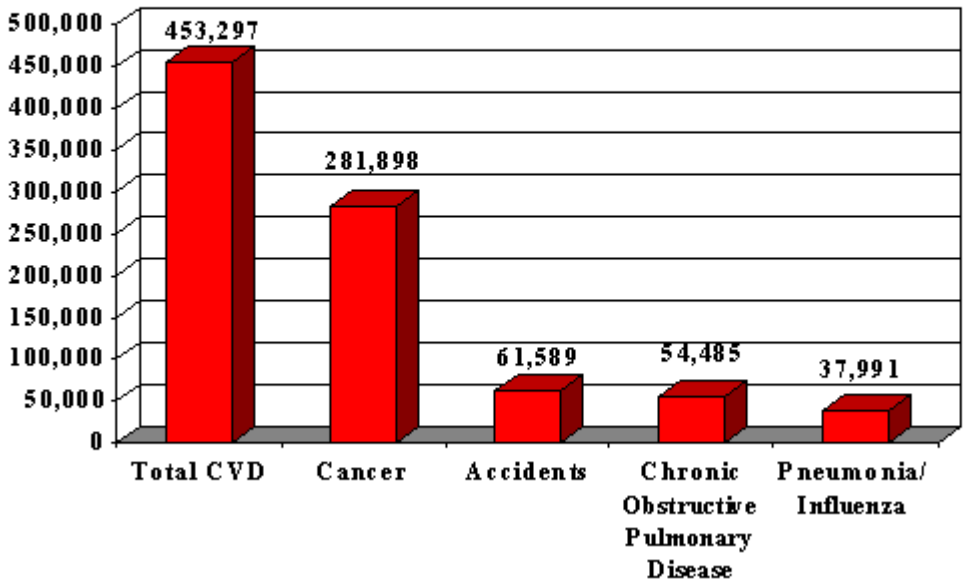
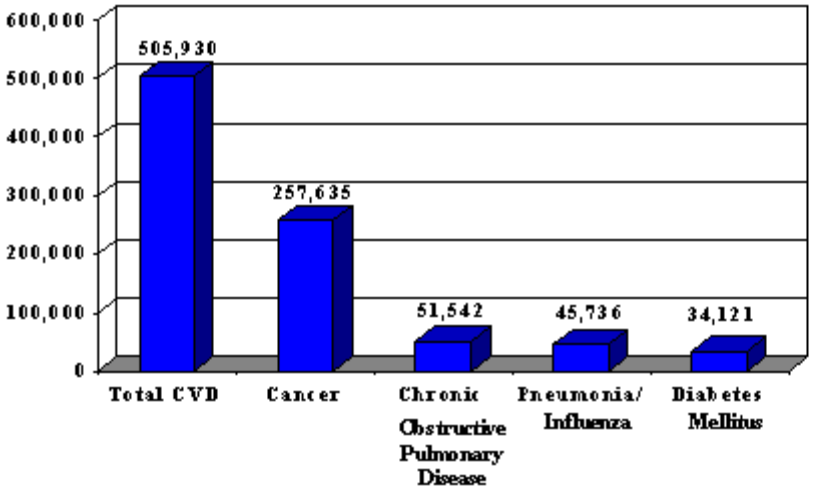


Table 2. Causes of Female Deaths in the U.S. (1997)



In all of its manifestations, including stroke, congenital heart disease, and hypertension, CVD accounts for fully 50% of total mortality. The prevalence of heart disease increases for both males and females with advancing age (Table 3). Nevertheless, its occurrence is not insignificant in the younger patient. As reflected by the American Heart Association's statistics, 218,000 males and 74,000 females between 45 and 64 years of age per year will suffer a heart attack (Table 4). Moreover, approximately 1.1 million Americans will suffer a heart attack this year and of this number approximately 500,000 will die. Of additional importance is the fact that approximately one half of those suffering a heart attack have no prior history of heart disease.

During the last 30 years, there has been significant reduction in coronary artery disease mortality, but the extent of the problem is increasing due to the increased life span of the population. CVD, which includes coronary artery and cerebrovascular disease, results in more death, disability, loss of income, and reduced quality of life than all other classes of disease combined. Economically, the disease affects society in both the loss of productivity and the ever-increasing health care costs, now approaching over 100 billion dollars per year.

The reasons for the decline in mortality are not fully understood. Life-style changes, better medical surveillance, and better medical treatment probably account for this trend. Despite the drop in the death rate, the prevalence of CAD is still pandemic. Millions of individuals are now living with CAD and are certainly at risk for congestive heart failure, another heart malady whose incidence is trending upward.

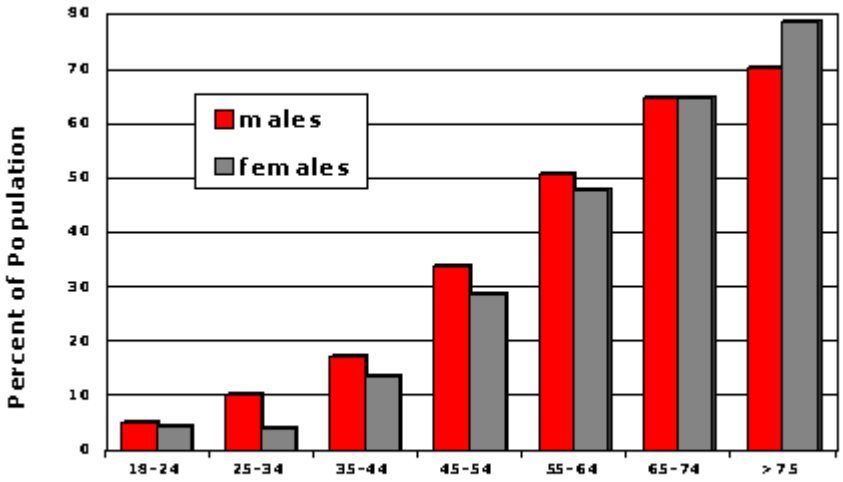


Table 3. Prevalence of Coronary Heart Disease

Cardiovascular disease has been described pathologically and clinically since the beginning of recorded medicine. Our understanding of cardiovascular disease is constantly undergoing change. The pathologic abnormalities of the heart and blood vessels of the body have been clearly documented to the cellular level. However, at this juncture we lack a complete understanding of the various disease states and their progression. In many cases, they are described only in speculative and theoretical models. Despite these limitations, our understanding of some of the disease states and their treatment has become highly advanced.

Arteriosclerosis is a generalized term for thickening or hardening of the arteries, which are the vessels supplying oxygenated blood and nutrients to all the tissues and organs of the body. Atherosclerosis is a more specific term applied to the buildup of plaque, which is composed of fatty or lipid-rich material within the internal layers of the medium and large diameter arteries. In the present chapter, we shall be mainly concerned with the more specific term—atherosclerosis—which particularly applies to the coronary arteries.

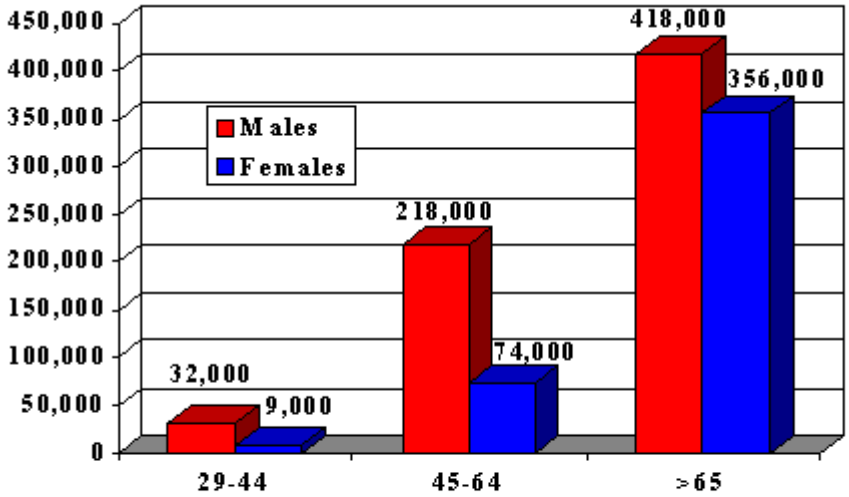


Table 4. Projected Annual Heart Attacks

The mechanism of atherosclerosis starts with an injury on the arterial wall. Circulating blood products, including platelets and fibrin, deposit in the injury. Over time, there is a deposition of fatty molecules, particularly cholesterol. The earliest actual lesion is a fatty streak, believed to be the earliest demonstrable evidence of atherosclerosis. Over time, the fatty streak becomes essentially irreversible. Abnormal proliferation in the number of cells occurs in the internal layers of the affected artery. Eventually, the deposits of fat accumulate and the cells enlarge, which sets up a reaction that causes the lesion to thicken gradually and protrude from the internal layers of the arteries. This process produces organized scarred lesions or plaques. These plaques can enlarge into the lumen (tubular cavity) and partially obstruct the vessel, thus diminishing blood supply to the tissues and organs. Furthermore, blood clots, or thromboses, can form on these atherosclerotic lesions. The local blockage of the blood vessel causes a decrease in blood flow to the heart muscle. This may result in ischemia, the cutoff of oxygen and nutrients flowing to the heart muscle. This transitory lack of blood supply to the heart is often accompanied by chest pain (angina). If the blood supply is interrupted for long periods of time, irreversible heart damage may occur through a heart attack.

The characteristic pattern of atherosclerosis is the accumulation of fatty or lipid material in the inner layers of the large and medium sized arteries. There is a predilection for the disease process to occur in the arteries of the heart (coronary arteries), leg and groin (femoral arteries), and the neck (carotid arteries), as well as in the main artery leaving the heart (aorta). These vessels are most vulnerable to adverse local blood flow and pressure characteristics that tend to promote the disease.

Atherosclerosis is a disease of the young that clinically manifests itself in the middle and later years of life. An American male child has a one-in-five chance of developing clinical heart disease before the age of 65. Random autopsies on young soldiers killed during combat in the Korean and Vietnam conflicts revealed high percentages of early, and in some cases advanced, atherosclerosis—this in a presumed young and healthy population whose average age was 22.[1] Some 10% of the men had already developed severe artherosclerosis in the major coronary arteries (greater than 50% blockage of the artery). These initial landmark autopsy studies give credence to the notion that atherosclerosis begins at an early age. The precise mechanism that initiates and perpetuates the development and progression of the disease process is unknown. The two most commonly suspected culprits—fatty infiltration of blood vessels and arterial wall injury—are in all likelihood closely interrelated.

Atherosclerosis begins when there are certain elevations in various cholesterol components in the blood. Lipoproteins are the main source of cholesterol transport. High-density lipoprotein (HDL) is composed mostly of proteins that have great affinity for transporting cholesterol from tissues to the liver. Low-density lipoprotein (LDL), on the other hand, helps transport cholesterol from the manufacturing site, the liver, to the cell walls of the arteries. HDL thus serves to deter atherosclerosis by binding to the cholesterol and carrying it away from the arterial wall to the liver, where it is broken down and removed from the body. The HDL fragments may also compete with LDL for sites on the arterial wall, thus preventing cholesterol from entering the cells.

In contrast, LDL acts as an enhancer of atherosclerosis. It infiltrates the internal layers of the artery in areas where there had been microscopic wall damage or epithelial injury. Injuries on the vessel wall can be caused by various stresses, such as hypertension or the biochemical effect caused by carbon monoxide from cigarette smoke. Over time, this chronic damage causes degenerative changes within the arterial wall leading to platelet accumulation and smooth muscle proliferation. An interaction can occur between the lipoproteins carried in the blood and the cells lining the arterial wall. Atherosclerotic plaques thereby slowly develop. Plasma-secreting factors, platelets, and other stimuli are responsible for the formation of the clots that have been implicated in all stages of artherosclerosis. Components of the initial clot, formed mostly by platelets, can stimulate cellular proliferation on the arterial wall surfaces.

Our understanding is changing regarding the mechanism of an acute myocardial infarction and possible sudden cardiac death. We know that these untoward events can occur in the presence of non-obstructive atherosclerotic plaques. At a vulnerable site, these plaques can disrupt the thin fibrous cap over an artherosclerotic lesion. This event causes a rapidly occurring cascade of events leading in turn to vessel constriction and acute thrombosis that may result in fatal or non-fatal myocardial infarction. Local inflammation, acute cellular proliferation, and multitudes of mechanisms not understood are occurring in these dynamic and vulnerable lesions. Certain triggers seem to place these lesions at risk. They include acute rises in blood pressure and mechanisms that increase clot formation or coagulation (see Chapter 4). Standard coronary risk factors can also act as triggers, as well as complex stress mechanisms including circadian patterns of arousal.[2]

THE U.S. ARMY'S INTEREST IN CARDIOVASCULAR DISEASE

For over half a century, the U.S. Army has been interested in the detection, diagnosis, and treatment of CAD among the active duty and retired populations. These groups have experienced significant physical impairment and death from this disease, thus placing a huge financial and resource burden on the medical system, not to mention the strains imposed by the loss or incapacitation of experienced personnel still in their productive years. As mentioned earlier, on the basis of

random autopsies of young soldiers, military pathologists were able to establish that occult coronary atherosclerosis was occurring at very early ages, years before symptoms would have appeared. Ongoing military epidemiological studies have demonstrated the extent of both exercise and non-exercise coronary artery morbidity (disease) and mortality in the active Army population. This CAD death rate has been approximately one per 5,000 in the over-40 Army population, with an ever-increasing incidence in older age groups. Since 1981, the United States Army's Cardiovascular Screening Program has been a part of the physical exam for all soldiers. It has been designed to determine and treat an individual's CAD risk factors and to use non-invasive tests for higher risk sub-groups in order to identify the individuals who are at most risk for cardiac events.

Despite this endeavor, CAD remains the leading cause of morbidity and mortality in the middle-aged soldier. Clinically significant CAD usually manifests initially in post-menopausal women and over-40 men, steadily increasing in both groups thereafter. Likelihood of the disease is further increased by the presence of such risk factors as hypertension, smoking, elevated levels of cholesterol and triglycerides, diabetes mellitus, and family history of the disease.

In order to detect and prevent the progression from occult to symptomatic heart disease, Army physicians have relied on a variety of diagnostic techniques such as treadmill electrocardiography and angiograms. Since the summer of 1997, the Army has incorporated Electron Beam Computed Tomography (EBCT) in an all-encompassing preventive cardiology program called the Walter Reed Army Medical Center Heart-View EBCT. Through extensive medical promotion, the Heart-View EBCT program has become an active and sought-after cardiovascular screening program. This chapter will introduce the concept of EBCT, describe the Heart-View program, and discuss its utility as a key health screening initiative. Epidemiologic and demographic conclusions from the initial study of a patient population are reported, as well as early results of coronary calcium determination. Comparisons with previous literature and other populations are made, conclusions drawn, and recommendations suggested.

Evaluation of Coronary Artery Disease

When a physician considers evaluating patients for CAD, he or she is immediately confronted with the problem of segregating patients into those demonstrating symptoms such as angina and those who are asymptomatic. The symptomatic patient is evaluated in a relatively straightforward manner. This assessment includes a complete physical examination, including an evaluation of the patient's blood pressure, body weight, history of stress, physical activity, and family history. Laboratory parameters include serum cholesterol (both high-density and low-density cholesterol subtypes), fasting serum glucose, a resting electrocardiogram, and likely a treadmill exercise stress test (looking for electrical evidence for impaired blood flow to the heart). Often a patient will also undergo a thallium stress test, employing the injection of a radioactive isotope into the bloodstream and subsequent evaluation of the heart's ability to pump in the face of increasing levels of exercise. Finally, an invasive procedure known as a coronary angiography may be performed. This involves placement of a small catheter and injection of a radiopaque contrast material into the coronary circulation and subsequent imaging of the arteries to look for obstruction or blockage. Also available is a technique called intravascular ultrasound, also invasive, that employs the placement of a small ultrasound-tipped catheter into the coronary circulation for the purposes of measuring the presence of plaque on the interior walls of the arteries. Both of these techniques are expensive, and not without some risk to the patient. These techniques are appropriate for the symptomatic patient, but because of their invasiveness and expense are ill-suited for screening a population of asymptomatic individuals who possess one or more risk factors. EBCT is in a unique position to evaluate the coronary circulation in these particular patients.

EBCT is a simple, non-invasive, rapid scanning device that can provide an accurate quantitative measurement of coronary artery plaque. This information is a valuable component in a comprehensive evaluation of overall cardiac status, complementing the physical examination and other laboratory studies performed by the primary care physician.

EBCT: THE THEORY

Of great importance in the detection of early atherosclerotic changes in coronary circulation is the association of coronary artery calcification with the disease process. Numerous studies have clearly and unequivocally established a direct relationship between coronary artery calcification and the pathologic presence of atherosclerotic heart disease. The presence of coronary artery calcification correlates in a fairly linear relationship with the volume of coronary artery plaque. Additionally, there is a direct association between coronary calcium and both the location and extent of atherosclerotic plaques within the coronary circulatory system. The association between coronary artery calcification and atherosclerotic plaque formation within the coronary vessels has long been a staple of the Army screening program for heart disease, which used cardiac fluoroscopy as a means of detection. As will be shown below, the emergence of EBCT offers superior capabilities in the identification, quantification, and location of coronary plaque disease. This calcium marker encompasses approximately 20% of all coronary plaque, forming the basis of the EBCT screening method for CAD.

Conventional computed tomography is a primary tool in the diagnostic armamentarium of the radiologist. Over 13,000 of

these examinations are performed at Walter Reed Army Medical Center on a yearly basis. Conventional computed tomography uses a focused x-ray beam and a detector array, with both moving around the patient in a circular fashion as the patient moves past the x-ray source and detector array. This process can be time-consuming. Unlike conventional computed tomography, however, EBCT offers the advantage of ultra-fast capabilities.

Although appearing somewhat similar to conventional computed tomography in its outward appearance (see Fig. 1), the inner workings of EBCT essentially involve the generation of a high-speed stream of electrons which are focused on 1-4 target rings situated below the patient. When bombarded by electrons, these target rings generate a highly focused, parallel ray beam of x-rays through approximately a 30-degree arc, which electronically moves through the patient. With the exception of the patient-moving shelf carrying the patient through the focused field of generated x-rays, there are no moving parts. By combining this process with a triggering mechanism timed to the electrocardiogram, it is possible to get extraordinarily detailed and motion-free images of the heart and the coronary circulation non-invasively and in a matter of seconds. The entire examination is routinely accomplished in less than a minute and requires no sedation or the injection of any material into the patient. Because of its exceptional spatial and temporal resolution and the intrinsic ability of computed tomography to identify regions of varying tissue density (i.e. calcium), EBCT can evaluate with great accuracy the epicardial coronary arteries and the presence of coronary calcification within them.

EBCT: INTERPRETING THE DATA

Approximately 15 years ago, A. S. Agatston and colleagues devised a method to quantify the presence of coronary calcification in all of the main epicardial coronary arteries and generate an overall coronary calcium score.[3] This score has been validated in over 19,000 patient examinations and is the technique utilized in the Heart-View Early Diagnosis and Screening Service at Walter Reed Army Medical Center. In considering the performance of EBCT regarding the coronary arteries and the application of the Agatston criteria for coronary calcium scoring, it is important to bear in mind that the presence of coronary artery calcium equals the presence of atherosclerotic coronary artery disease—there are no mimics. The presence of coronary calcification as determined by EBCT equals coronary atherosclerosis. The greater the degree of coronary calcification, the greater the degree of atherosclerotic heart disease present. The technique is both sensitive and specific for the detection of coronary calcification, its extent, and its distribution.

These studies firmly established the prognostic role of the coronary calcium score as determined by the Agatston criteria. Clinical experience has demonstrated that there is a direct correlation between the calcium score in an asymptomatic population and the subsequent development of symptomatic cardiovascular disease. Recently, three large clinical studies were performed evaluating the prognostic capabilities of coronary screening using the EBCT calcium score. Asymptomatic patients undergoing EBCT were monitored for periods ranging from 19 to 72 months.

Figure 1. **EBCT Scanner Appearance**

For example, R. Detrano and associates evaluated the prognostic value of coronary calcium scoring for predicting coronary heart disease or heart-related events in 491 patients with a mean age of 55 plus or minus 12 years.[4] All of these individuals underwent coronary angiography as well as EBCT. The EBCT coronary calcium scores were divided into quartiles. Odds ratios were calculated for all cardiac events during the follow-up period of 30 months plus or minus 13 months. Those individuals scoring above the 75th percentile (i.e. those with high coronary calcium), compared with those scoring below the 25th percentile (i.e. those with low calcium) demonstrated an odds ratio of 10.8 with 95% confidence. This means those in the high-calcium quartile were approximately 11 times more likely to have a cardiac event during the follow-up period.

Y. Arad and associates followed 1,173 patients who were asymptomatic at the time of the examination with a mean age of 53 years plus or minus 11 years.[5] After approximately 3.6 years of follow-up, those individuals scoring greater than 160 on their composite calcium score had an odds ratio of developing symptomatic cardiovascular disease of 23 to 1. Agatston and associates followed 367 asymptomatic men and women with a mean age of 52 years for a period of between 36 and 72 months. The odds ratio for the development of asymptomatic coronary artery disease was 6.9 to 1 with 95% confidence for those with an initial calcium score greater than 50, and 2.7 to 1 with 95% confidence for those with a calcium score between 1 and 14.[6] This means that those individuals having the highest calcium scores had a risk of developing coronary heart disease more than 10 times that of those scoring in the lowest quartile.

These and other studies support the concept that coronary artery calcification is correlated with a measurable risk of a definable ischemic cardiac event (i.e. myocardial infarction, heart attack, or occlusion requiring coronary artery bypass surgery) occurring between 19 and 72 months from the time of the examination. Moreover, it was found that the risk of symptomatic cardiovascular disease is proportional to the EBCT total calcium score.

J.A. Rumberger and colleagues recently published a review in the *Mayo Clinic Proceedings* of the literature and guidelines for the use of EBCT and the coronary calcium score in the evaluation of asymptomatic persons.[7] These guidelines divide the calcium scores into five categories. As can been seen from Table 5, a score of 0 indicates the presence of no identifiable calcified atherosclerotic plaque. This shows a very low probability of the presence of significant coronary artery disease in the individual and likewise a very low risk of the near term development of significant or symptomatic CAD. In sum, the EBCT calcium score identifies a relative plaque burden, described as none, minimal, mild, moderate, or extensive—and also indicates the probability of significant CAD being present or developing in the near term.

Calcium score	Diagnosis	Clinical Interpretation
0	No identifiable atherosclerotic plaque. Very low CV risk.	A "negative" examination. Probability >90-95% for absence of "significant" CAD
1 to 10	Minimal plaque burden. Low CV risk.	"Significant" CAD very unlikely.
11 to 100	Mild, plaque burden. Moderate CV risk.	Likely mild or minimal coronary stenoses.
101 to 400	Moderate plaque burden. High CV risk.	Moderate non-obstructive CAD highly likely.
Over 400	Extensive plaque burden. Very high CV risk.	High likelihood of at least one "significant" coronary stenosis.

Table 5. EBCT Calcium Score Interpretation Guidelines

The guidelines set forth by Rumberger also contain recommendations for patient management, including medical and dietary treatment of elevated cholesterol. These recommendations are based on the National Cholesterol Education Program, Adult Treatment Panel #2, dealing with the detection, evaluation, and treatment of high blood cholesterol in adults. It should be noted that a negative or extremely low calcium score (i.e. below a score of 10) does not and cannot totally exclude the presence of coronary atherosclerosis. However, it does establish the absence of fixed or significant obstructive coronary disease with 90-95% confidence.

EBCT: THE WALTER REED ARMY MEDICAL CENTER EXPERIENCE

The Department of Radiology at Walter Reed Army Medical Center (WRAMC) instituted the Heart-View Cardiac Screening Program as part of the Early Diagnosis and Screening Service within the Department in 1997. Under the direction of Dr. Irwin Feuerstein, who directed EBCT Research at the National Institutes of Health for over 10 years, the program performed some 6,500 examinations during the first 2 years of its operation. These examinations have been performed on active duty service members, spouses, and retirees. Also, because of its special pediatric applications, a number of examinations have been performed on children as young as 10 weeks of age. The total service provides evaluation, counseling, and referral by an expert team including computed tomography technologists, nurse counselors, and a clinical cardiology consultant. The program has employed the Agatston method of coronary calcium scoring and the Rumberger guidelines since the program's inception. Approximately 80% of our patients have been male and 20% female, with the percentage of female patients rising with the age category. Approximately 35% of our first 1,000 patients examined were between the ages of 40 and 50 years of age, 43% between 51 and 60, and 12% between 61 and 70. For the most part the health of our population has been somewhat better than the overall health of the general population. For example, only 19% of the patients seen at WRAMC scored in the highest general population quartile for disease and subsequent risk. Only 15% of men less than 45 and 7% of women less than 45 were in the highest quartile for disease. Between the ages of 46 and 50, 24% of men and only 12% of women were in the highest quartile for disease. Between the ages of 51 and 55, 18% of men and 16% of women were in the highest general population quartile for disease.

The screening service is also at the center of a number of clinical investigations involving an analysis of the incidence and prevalence of CAD in the active duty population, the potential evolution of this disease process, and the efficacy of efforts to slow or reverse it. Investigations are also being conducted to evaluate the usefulness of the EBCT calcium score in modifying patient behavior so as to minimize risk factors of coronary heart disease.

A fundamental mission of the military healthcare system is to preserve the fighting strength of the armed forces so that they will be fit enough to win the nation's wars. Performance, deployability, and sustainability are all essential interrelated factors in this equation. The Heart-View Early Diagnosis and Screening Service is involved in every level of this effort.

EBCT: ROLE IN THE GENERAL POPULATION

The ability to diagnose and treat CAD has enormously improved over the last two decades. This improvement has occurred on several fronts. There has been a substantial and far reaching public health effort directed toward education of patients regarding the signs and symptoms of an acute heart attack, thus prompting earlier medical intervention. Smoking awareness programs and education on the role of diet and exercise in the development of CAD have greatly expanded. For example, the role of pharmacologic intervention in smoking cessation has helped decrease the use of tobacco and tobacco products in some groups. Improved knowledge and awareness of the roles of elevated cholesterol and some elevated blood lipids, as well as familiarity with lipid-lowering drugs (e.g. the statins) have all impacted favorably on the prevalence of coronary heart disease. The role of aspirin both in primary prevention and in decreasing the risk of a second myocardial infarction has been promoted. The acute management of myocardial infarction has also undergone tremendous evolution in the form of pharmacologic clot-busters aimed at relieving the obstruction to blood flow. Thrombolitic therapy has become a major therapeutic advance in the treatment of acute myocardial infarction.

All of these measures have served to improve general prospects for treating acute coronary heart disease. Nonetheless, the disease remains the number one cause of death in the United States. Although most of our active duty force is often regarded as "too young" for the development of CAD, much evidence supports the supposition that this process is of lifelong duration, beginning in childhood. As is apparent from the figures presented above, CAD often manifests itself in the fifth and even the fourth decade of life. It is thus incumbent upon the organizational health care system to pursue the optimum evaluation and treatment of this disease.

WHO SHOULD RECEIVE THE EBCT CARDIAC SCREENING EXAMINATION?

If you have one or more of the following risk factors for coronary disease, the EBCT examination may be of benefit to you in identifying the potential presence of CAD and determining its relative severity:

- A positive family history for heart attack
- Men over 40 years of age or post-menopausal women
- Smoking history
- Elevated cholesterol
- History of high blood pressure or hypertension
- Overweight by more than 20% of your ideal body weight
- Previous heart attack
- Any existing symptom of cardiac disease, i.e. heaviness or pressure in the chest with exercise, or shortness of breath with minimum exertion such as climbing a flight of stairs.

EBCT can provide important information regarding the relative severity of the disease process as well as its location and distribution within the coronary artery system in a noninvasive way. It can provide valuable information regarding the overall prognostic implications of the patient's condition. It can also serve as a useful tool in helping to determine what patients require more or less vigorous intervention in the form of lipid-lowering medications, the use of aspirin, or other treatment regimens. Electron Beam Computed Tomography can also help to determine which patients would benefit from further diagnostic testing, thallium stress testing, and possibly coronary angiography. Preservation of health and well-being for the soldier and the soldier's family is fundamental to preserving the nation's fighting strength. The early diagnosis of coronary artery disease is essential if this goal is to be realized.

ENDNOTES

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